Temporal precedence of emotion over attention modulations in lateral amygdala: Intracranial ERP evidence from a patient with temporal lobe epilepsy

Gilles Pourtois[1], Laurent Spinelli[4,5], Margitta Seeck[4,5], & Patrik Vuilleumier[2,3]

(1) Department of Exp. Clinical and health psychology, Ghent University, Belgium

(2) Laboratory for Behavioral Neurology & Imaging of Cognition, Department of Neuroscience & Clinic of Neurology, University of Geneva, Geneva, Switzerland

(3) Swiss Center for Affective Sciences, University of Geneva, Geneva, Switzerland

(4) Pre-surgical Epilepsy Evaluation Unit, Clinic of Neurology, University Hospital, Geneva, Switzerland

(5) Functional Brain Mapping Laboratory, Department of Neuroscience, University of Geneva, Geneva, Switzerland

Correspondence :

Gilles Pourtois

Department of Experimental clinical and health psychology

Ghent University

Henri Dunantlaan 2

9000 Gent, Belgium

Phone: +32 9 264 9144

Email: gilles.pourtois@ugent.be

Abstract

Previous fMRI studies reported mixed evidence for the influence of selective attention on amygdala responses to emotional stimuli, with some studies showing "automatic" emotional effects to threat-related stimuli without attention (or even without awareness), but other studies showing a gating of amygdala activity by selective attention with no response to unattended stimuli. We recorded intracranial local field potentials from the intact left lateral amygdala in a human patient prior to surgery for epilepsy and tested, with a millisecond time-resolution, for neural responses to fearful faces appearing at either task-relevant or task-irrelevant locations. Our results revealed an early emotional effect in the amygdala arising prior to, and independent of, attentional modulation. However, at a later latency, we found a significant modulation of the differential emotional response when attention was directed towards or away from fearful faces. These results suggest separate influences of emotion and attention on amygdala activation, and may help reconcile previous discrepancies concerning the relative responsiveness of human amygdala to emotional and attentional factors.

Keywords: emotion, attention, emotional attention, intracranial recordings, ERP

Introduction

The rapid detection of threat is crucial for the organism's survival. Converging evidence from behavioral (see Ohman & Mineka, 2001; Anderson, 2005), neurophysiological (LeDoux, 1996), neuropsychological (Vuilleumier & Schwartz, 2001; Anderson & Phelps, 2001) and brain-imaging (Vuilleumier, Armony, Driver, & Dolan, 2001; Dolan & Vuilleumier, 2003; Vuilleumier, 2005) studies lends support to the hypothesis that the human brain is equipped with specific mechanisms to swiftly appraise threat-related stimuli in the environment and engage attentional resources towards them so as to allow adaptive behaviors. These mechanisms are thought to be crucially dependent on the amygdala function and to subserve a distinct process of *emotional attention* (Vuilleumier, 2005), affording the capture of attention by unattended but emotionally-relevant stimuli, through neural pathways that are separate from those controlling voluntary visuo-spatial attention. The amygdala is known to play a predominant role in emotional processing and learning (see Phelps, 2006). Moreover, lesions of the amygdala have not only been shown to impair fear recognition in humans (Adolphs, Tranel, Damasio, & Damasio, 1994; Adolphs, Tranel, Damasio, & Damasio, 1995; Calder, Lawrence, & Young, 2001), but also to reduce threat-related activations in remote brain regions of the infero-temporal and parietal cortex (Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004), which are presumably subserving mechanisms of emotional attention via feedback connections received from amygdala (Surguladze et al., 2003; Sabatinelli, Bradley, Fitzsimmons, & Lang, 2005; Amaral, Behniea, & Kelly, 2003; Vuilleumier & Driver, 2007).

Consistent with such a role for efficient threat detection, the amygdala response to emotional stimuli has been found to arise automatically, without explicit attention to the

stimuli or sometimes even without awareness (LeDoux, 1996; Whalen et al., 1998; Morris, Ohman, & Dolan, 1999; Ohman & Mineka, 2001; Anderson & Phelps, 2001; Morris, DeGelder, Weiskrantz, & Dolan, 2001; Dolan & Vuilleumier, 2003; Pasley, Mayes, & Schultz, 2004; Williams, Morris, McGlone, Abbott, & Mattingley, 2004; Jiang & He, 2006). However, the current evidence still remains highly contentious as to whether emotional processing in the amygdala is dependent on selective attention (Pessoa, McKenna, Gutierrez, & Ungerleider, 2002). Conflicting results have been observed by some fMRI studies that systematically manipulated attention to emotional stimuli, some suggesting that amygdala may activate to fearful faces both within or outside the current attentional focus (Vuilleumier et al., 2001; Vuilleumier et al., 2004; Anderson, Christoff, Panitz, De Rosa, & Gabrieli, 2003; Pasley et al., 2004; Williams et al., 2004), and others reporting abolished responses for unattended or masked threat-related stimuli (Pessoa, McKenna et al., 2002; Pessoa, Padmala, & Morland, 2005; Pessoa, Japee, Sturman, & Ungerleider, 2006). Still other studies reported decreased responses to threat stimuli but increased responses to neutral or positive stimuli (Williams, McGlone, Abbott, & Mattingley, 2005; Silvert et al., 2007). However, given its sluggish temporal resolution (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001), BOLD-fMRI cannot unequivocally establish if emotional and attentional effects actually occur in the amygdala but during distinct time periods, as predicted by models postulating rapid inputs to the amygdala prior to full attention (see Cowey & Stoerig, 1991; LeDoux, 1996; Morris et al., 1999; Bar et al., 2001; Vuilleumier, 2005). Thus, based on the current evidence, a possible prediction (Vuilleumier, 2005) could be that an early stimulus-driven response to emotional information might take place in the

amygdala irrespective of attentional control (see also Vuilleumier, Armony, Driver, & Dolan, 2003; Whalen et al., 2004; Dolan & Vuilleumier, 2003), whereas selective attention might modulate the level of amygdala activation (and hence gate the processing of threat-related stimuli) during a later time-period, consistent with the effects of top-down regulatory influences exerted on visual pathways by higher-level cortical regions involved in attentional control, such as the fronto-parietal network (see also Armony & Dolan, 2002; Krolak-Salmon, Henaff, Vighetto, Bertrand, & Mauguiere, 2004; Pourtois, Schwartz, Seghier, Lazeyras, & Vuilleumier, 2006; Vuilleumier & Driver, 2007).

Existing data are still scarce regarding the time-course of activation to threat-related stimuli in the human amygdala, in contrast to numerous neurophysiological studies that focused on this structure in non-human primates (Amaral et al., 2003). Several neurophysiological studies have contributed to better characterize some response properties of the amygdala in non-human primates, most notably by recording early category-selective responses to faces (see Leonard, Rolls, Wilson, & Baylis, 1985; Nakamura, Mikami, & Kubota, 1992; Hoffman, Gothard, Schmid, & Logothetis, 2007) and by showing its ubiquitous involvement in aversive fear conditioning (LeDoux, 1996; Phelps & LeDoux, 2005; Samson & Pare, 2006). By contrast, only a few human studies have used intracranial recordings to examine the time-course of activation of the human amygdala to visual threat-related stimuli, such as fearful faces (see Halgren et al., 1994; Fried, MacDonald, & Wilson, 1997; Krolak-Salmon et al., 2004). Some of these studies looked at the spiking activity of single neurons and disclosed highly-circumscribed stimulus-driven category-selective responses in the amygdala (as well as hippocampus) to various combinations of facial expressions and identities (Fried et al., 1997; see also

Kreiman, Koch, & Fried, 2000); whereas other studies recorded intracranial local field potentials (iLFPs) to demonstrate that the human amygdala could differentiate between neutral and fearful faces after 200 ms post-stimulus onset (Krolak-Salmon et al., 2004).

Noteworthy, Krolak-Salmon et al. (2004) also reported that an early differential neural activity in the amygdala around 200 ms arose for fearful relative to happy, neutral or disgusted faces, but only when the patients were asked to attend to the facial expression content (i.e., to count faces expressing surprise), not when the patients performed a gender discrimination task (i.e., to count male or female faces). This dissociation suggests a task-dependent modulation of this relatively early threat-related processing in the amygdala. However, these results contrast with several fMRI studies showing reliable activation to fearful faces when healthy observers process non-emotional faces including gender discrimination (Morris et al., 1996; Phillips et al., 2001; Vuilleumier et al., 2003), including in studies that directly compared explicit and implicit processing of emotion expressions (Critchley et al., 2000). Furthermore, this earlier intracranial study did not assess the effects of emotional expressions (fearful vs. neutral) and selective attention (spatially attended vs. unattended faces) within the same task (see Vuilleumier et al., 2001) so as to test whether distinct effects of emotion and attention could be detected in the amygdala, or whether, alternatively, attentional effects precluded all (including early) emotional effects in this region. Only task demands were manipulated in this study (Krolak-Salmon et al., 2004). Because the patients' performance on the facial expression task was worse (88% correct) than the gender discrimination task (99% correct) (Krolak-Salmon et al., 2004), this factor could at least partly contribute to the reported difference in amygdala responses between these two

tasks (see also Pessoa, McKenna et al., 2002). Hence, it remains unclear whether emotional and attentional effects may actually occur in the same amygdala region but during distinct time periods (as predicted by some models, e.g. see Vuilleumier, 2005), or instead, whether attentional control can merely suppress the early emotional response of the amygdala under some circumstances (in accord with a selective gating of emotional processing by selective attention in this brain structure, e.g. see Pessoa, Kastner, & Ungerleider, 2002; Pessoa, McKenna et al., 2002).

We had the opportunity to address this question by recording iLFPs, with a millisecond time-resolution (Logothetis et al., 2001), from face-selective contacts in the left lateral amygdala of a unique human patient with medically refractory epilepsy (Fig. 1a). Patient CT was selected for our study because he had structurally intact left temporal lobe and amygdala (see case description here below). Recordings were performed during the same task as used in several previous fMRI studies (Vuilleumier et al., 2001; Vuilleumier et al., 2004; Bentley, Vuilleumier, Thiel, Driver, & Dolan, 2003; Bishop, Duncan, & Lawrence, 2004; Silvert et al., 2007), in which pictures of fearful or neutral faces were shown together with pictures of houses while attention was directed either to faces or houses. Thus, the task-demands were kept unchanged between conditions where faces were presented at task-relevant and -irrelevant positions, respectively. On any given trials, neither the relevant stimulus category (face or house) nor the emotional face expression (fearful or neutral) could be predicted, allowing an assessment of purely stimulus-driven responses. This paradigm therefore provides a 2 x 2 factorial design allowing us to test for the main effects of emotion vs. attention on neural responses to faces, as well as any interaction between these factors. Several fMRI studies using this

paradigm in healthy participants have found amygdala activation to fearful faces regardless of whether faces were task-relevant or -irrelevant in this task (Vuilleumier et al., 2001; Vuilleumier et al., 2004; Bentley et al., 2003; Bishop et al., 2004; but see also Silvert et al., 2007). Based on these results, we hypothesized that an early (<200 ms post-stimulus onset, see Krolak-Salmon et al., 2004) differential response to fearful vs. neutral faces should occur in the amygdala regardless of whether faces were task-relevant or irrelevant. In addition, based on other results suggesting some attentional gating in the amygdala (see Pessoa, McKenna et al., 2002), we also surmised that some difference might arise at a later latency when face stimuli were task-relevant rather than irrelevant (see Krolak-Salmon et al., 2004; Vuilleumier, 2005).

Methods

Case description

Patient CT was a 30-year-old right-handed male, with a clinical diagnosis of cryptogenic complex partial epilepsy since 15 years. His seizures (frequency: 0 to 5 episodes per month) were characterized by transient losses of consciousness, followed by post-ictal decrease of verbal memory performance. Detailed neurological assessment showed no cognitive impairment between seizures, and the patient worked normally as an employee in an international organization. He was treated with a regular anti-epileptic drug (leviracetam), which was interrupted after electrode implantation according to a standard weaning protocol. All our investigations were performed during the pre-surgical evaluation phase in the regular clinical setting, while the patient underwent intracranial

EEG with depth electrodes in the left temporal and frontal lobes to identify the epilepsy focus (Seeck et al., 1995; Seeck et al., 2001). A written informed consent was obtained from the patient prior to his participation to this study, following the standard practice in the pre-surgical evaluation unit (Department of Neurology, University Hospital, Geneva). This research was approved by the local ethical committee. This patient was selected for our experimental protocol based on the following criteria: (i) no interictal cognitive deficit and a normal ability to perform our demanding attention task; (ii) at least one electrode implanted in an intact amygdala, with no clinical evidence of structural or epileptic anomalies at the recorded site (Fig. 1a); (iii) reliable stimulus-driven responses recorded from at least one electrode contact in the amygdala; (iv) no subclinical seizure observed during our intracranial recordings.

Stimuli and experimental tasks

The patient participated in two separate experiments, a localizer task and a main attentional task. The aim of the localizer task was to obtain independent evidence (using a separate set of face stimuli and another task) to demonstrate the selectivity and location of the (left) amygdala responses to faces (relative to houses). Next, the patient performed the main (attention) matching task (Vuilleumier et al., 2001), in which we could examine the processing of fearful faces in face-sensitive contacts of the left amygdala, contrasting two different attentional conditions (when fearful faces were either task-relevant or task-irrelevant).

In the two experiments, visual stimuli were shown on a computer screen at a viewing distance of about 1 meter, with its center roughly aligned with the eyes level.

Pictures were presented against a homogenous dark background and had a similar size across all experiments [400 (width) x 540 (height) pixels on a 1024 x 768 resolution screen]. Pictures covered approximately 8 x 11 degrees of visual angle. Average luminance of stimuli was ~25 cd/m^2.

In the localizer experiment, the patient was shown pictures of a single neutral face or single house with varying viewpoints, presented in a continuous block of 90 stimuli (45 per condition, in random order, stimulus duration 400 ms; fixed ISI: 3500 ms). The patient was instructed to report any immediate repetition of the same stimulus (one-back repetition task, 12 immediate repetitions in total, performance 99% correct).

In the main (attention) experiment, the patient viewed brief (750 ms) visual displays comprising two faces (either fearful or neutral) and two houses in vertical and horizontal pairs (see Vuilleumier et al., 2001 for additional details about the stimuli). The position and expression of faces varied pseudo-randomly across successive trials. ISI was kept constant (3500 ms). The patient fixated a central point and was instructed to concentrate on either the vertical stimulus pairs (first block) or the horizontal stimulus pairs (second block), in order to judge whether the two stimuli at these locations matched or not (i.e., whether the two faces were the same or different, or whether the two houses were the same or different). Orthogonally to this, the expression of faces was either fearful or neutral, regardless of whether attention was focused on the face pairs (faces relevant) or on the house pairs (faces irrelevant). Each block comprised 96 trials, with the two object categories (faces vs. houses) and their locations fully randomized and counterbalanced across trials, resulting in a total of 24 neutral and 24 fearful faces at task-

relevant locations, and the same number for each expression at task-irrelevant locations (Vuilleumier et al., 2004).

Intracranial recordings

Intracranial local field potentials (iLFPs) were continuously recorded (Ceegraph XL, Biologic System Corps.) with a sampling rate of 512 Hz (bandpass 0.1–200 Hz) using several depth electrodes (AD-Tech, electrode diameter: 6 mm, inter-electrode spacing: 10 mm). LFPs reflect dendritic inputs and processing to a higher degree than the spiking output of a region (unlike single or mulit-units recordings that are still rarely performed in human patients, but see Fried et al., 1997), but correspond to signals recorded with scalp EEG and correlate with BOLD responses in fMRI (Logothetis et al., 2001). Although the biophysical origin of spiking activity is well understood, less is known about the origin of LFPs. LFPs arise largely from dendritic activity over large brain regions, and provide a measure of the input to and local processing within an area. Hence, the LFP constitutes a collective property of a neuronal ensemble (probably spanning several millimeters) and not a property of individual neurons. The primary component measured by the LFP in cortex is thought to be the excitatory postsynaptic potentials of dendrites, plus afterhyperpolarizing potential and afterdepolarizing potential. In other words, the LFP likely reflects subthreshold activity from a large group of surrounding neurons.

The reference electrode was located at position Cz and the ground at position FCZ in the 10–20 international EEG system. Intracranial visual evoked potentials were obtained by averaging LFPs time-locked to stimulus onset, for each stimulus category

separately. Individual epochs were low-pass filtered using a 30Hz cutoff. Electrode positions within the brain were determined by a CT-scan performed after implantation, coregistered with a high-resolution T1 MRI image using SPM5 (www.fil.ion.ucl.ac.uk/spm/software/spm5/), and then normalized to define Talairach coordinates of each of the electrode sites (see Fig. 1a).

Statistical Analyses of iLFPs

Single-trial EEG epochs were analyzed offline, after removing all epochs where propagation of epileptic spikes (from -500 to +1000 ms around a stimulus onset) might have spread to mesial temporal lobe and contaminated the recorded sites (~40%, using stringent criteria). In addition, we also eliminated single-trial EEG epochs containing homogenous epileptic bursts, or high-frequency noise. The number of spike-free trials subsequently used for statistical analyses was roughly similar for the different stimulus conditions, both in the localizer experiment (Fig. 1d; faces: 28 trials; houses: 28 trials) and in the main experiment (Fig. 2c; fearful faces attended: 28 trials; neutral faces attended: 24 trials; fearful faces unattended: 32 trials; neutral faces unattended: 29 trials). The amplitude variance computed for each time-point across these spike-free trials was used as the dependent variable for all statistical comparisons.

To determine whether amygdala responses were stable over time and across trials, we first computed an amplitude×time image for all presentations of stimuli (Delorme & Makeig, 2004), sorted in the consecutive order of trials for each experimental condition (see Fig. 1d and Fig. 2c). We also compared the variance (i.e., standard deviation) at each time frame (from -200 to + 1000 ms around stimulus onset) across the four experimental

conditions in order to assess whether this parameter varied or not. Inspection of variance across time points (and conditions) confirmed that it was stable and comparable, and that variability or non-linearity of activity did not create potential drifts in the "background" signal. These auxiliary analyses therefore confirmed that slight variations in the background signal across single trial data (see Fig. 1d and Fig. 2c) could not bias the results in any obvious manner.

The presence of significant difference between conditions (e.g. face/house, or emotion/attention modulations) was verified by nonparametric statistical analyses based on stringent randomization tests (see Manly, 1991 and Pourtois, Peelen, Spinelli, Seeck, & Vuilleumier, 2007 for a recent application with human intracranial data), allowing reliable inferences for single-subject data. Randomization provides a robust non-parametric statistical method without any assumption regarding data distribution, which compares the observed dataset with random shuffling of the same values over many iterations (i.e. permutations). The method runs by repeating the shuffling many times so as to be able to estimate the probability (here $p < 0.05$) that the data might be observed by chance. In accord with standard procedure used elsewhere (e.g. Pourtois et al., 2007), the significant alpha cutoff was set to $p<.05$, with an additional criterion of temporal stability for 5 consecutive time-points (>10 ms at 512 Hz sampling rate). We used a standard algorithm for permutations applied to the amplitude values of single trial iLFPs: an empirical distribution of the possible average amplitudes was estimated by (1) re-assigning single-trial amplitude values to different experimental conditions (i.e. permutations of the data), (2) recalculating the average amplitude, and (3) recalculating the resulting amplitude difference for these 'new' average amplitude values. Note that the

number of permutations that can be made with a group of n single-trial is 2^n, although Manly (1991) suggested that 1000-5000 permutations can be sufficient. Here we used a systematic number of 5000 permutations. The mean amplitude value from the actual data was then compared with the values from the empirical distribution to determine the likelihood that the empirical distribution had a value higher than the amplitude value from the actual data. This procedure was then repeated for each time point (time frame).

The onset latencies of negative deflections were determined by computing when iLFP amplitudes at each time-frame after stimulus onset differed ($p<.05$) from baseline values (defined as the mean activity from -200 ms to stimulus onset). All statistical analyses of iLFP data were performed using the Cartool software (developed by Denis Brunet, http://brainmapping.unige.ch/Cartool.php).

To provide another estimate of the reported differences, we also computed the mean amplitude of neural responses for each individual trial in the 140-280 ms time-interval post-stimulus (corresponding to the emotion effect, see Fig. 2a) and submitted these values to a receiver-operating curve (ROC) analysis contrasting fearful to neutral faces (irrespective of whether these faces were task-relevant or irrelevant).

Results

Behavioral results

Patient CT was highly accurate in all conditions of the attention task (mean 95% correct for face trials, 97% for house trials), suggesting a balanced task performance for faces and houses.

A conventional analysis of variance (ANOVA) was performed on single-trial RT data. Although a potential problem of ANOVA applied to single-subject data is the likelihood of serial correlation (i.e. between successive points), our experimental design minimized for any serial correlations by using a standard procedure to control for interrelated temporal sequence. First, the order of presentation of trials from the four conditions was randomized, so as to break up the serial correlation and obtain independence between samples. Second, we allowed ample time intervals between observations (fixed ISI: 3500 ms), which minimized serial correlations. This analysis showed that the patient was significantly slower to make same/different judgments on faces (857 ms) than houses [673 ms, main effect of attention condition, $F(1,44) = 114.86$, $p<.001$; see Fig. 1b], and generally slower on trials with fearful faces (task-relevant: 879 ms; task-irrelevant: 708 ms) than on those with neutral faces [task-relevant: 835 ms; task-irrelevant: 639 ms; main effect of emotion condition, $F(1,44) = 16.17$, $p<.001$; see Fig. 1b]. Thus, this emotion "negativity effect" (denoting a deeper processing of negative stimuli, see Cacioppo & Gardner, 1999) arose irrespective of whether faces were task-relevant or not [no interaction of attention x emotion, $F(1,44) = 1.60$, $p=.213$], replicating previous behavioral results obtained in normal adult healthy participants with this task (Vuilleumier et al., 2001). We also performed a complementary non-parametric statistical analyses (Friedman test) on the same RT data, which confirmed significant main effects of emotion ($p<.001$) and of attention ($p<.001$).

These behavioral results therefore suggest that fearful faces, even when being unattended, led to a different emotion processing than neutral faces. Importantly, differences in RTs between conditions did not account for differences in intracranial

ERPs, as demonstrated by auxiliary analysis on EEG epochs time-locked to motor responses (see below and Fig. 3d).

Intracranial results

We began by carefully characterizing the electrophysiological properties of amygdala responses to faces using an independent "localizer" experiment (neutral face vs. house stimuli). All statistical analyses were performed using stringent permutation tests. First, we found a typical biphasic negative deflection following stimulus onset (see Krolak-Salmon et al., 2004), that selectively arose at 3 adjacent electrode sites in left lateral amygdala (Fig. 1c), and whose amplitude started to differ from baseline after 136 ms for faces and 170 ms for houses ($p<.01$, Fig. 1c). Auxiliary and exploratory spectral analyses (data not reported here) indicated that this early negative activity corresponded to an event-related perturbation (Delorme & Makeig, 2004) arising primarily in the theta band, consistent with electrophysiological data on neuronal oscillations in the lateral nucleus of the amygdala in animals (~6 Hz, see Pare, 2003). This early activity was followed by more sustained category-related differences, with a lower amplitude of iLFPs for faces than houses from 230 to 480 ms ($p<.01$, Fig. 1c), and then a prolonged negative component to faces from 520 to 710 ms and a positive component to houses during the same period ($p<.01$, Fig. 1c). Reduced amplitude for faces in the latter two time-windows was compatible with an involvement of intra-amygdala inhibitory mechanisms after initial excitatory responses (Samson & Pare, 2006). Additional analyses verified that this activation to faces was stable across successive trials, without significant adaptation over

the course of our recording (see Fig. 1d) or any significant drift in the background signal (see Methods).

Based on these electrophysiological properties, we predicted that fearful expression and attention to faces should produce a selective modulation of activity at the same amygdala electrodes and within similar time-windows during our main experiment (Vuilleumier et al., 2001).

Recordings from face-sensitive sites in the lateral amygdala during the attention task showed an early and systematic differential neural response between fearful and neutral faces, regardless of attention (Fig. 2a, upper inset). A statistical comparison (non-parametric permutation test) between the two expressions, pooled across attention conditions, revealed significantly more positive iLFPs from 140 until 290 ms post-stimulus onset for fearful compared to neutral faces ($p<.01$), for the same three adjacent electrodes as above. This effect was highly similar for the three recordings sites (see Fig. 3abc). Post-hoc comparisons also confirmed that this early emotion effect was significant when faces were either task-relevant ($p<.05$) or task-irrelevant ($p<.05$). Furthermore, we also examined the reliability of the early emotion response by a receiver-operating curve (ROC) analysis on the mean iLFP amplitudes recorded for each individual trial during the 140-280 ms time-interval post-stimulus onset (see Methods and Fig. 3e). Results confirmed that the amplitude of neural responses for single trial data during this time-interval was reliably different between fearful vs. neutral faces (asymptotic significance, $p = .02$; area under the curve = .62).

Conversely, comparing trials with task-relevant vs. task-irrelevant faces (regardless of emotion expression) revealed a sustained attentional effect at the same

three face-sensitive electrodes in left amygdala, but starting at a later time-point 710 ms post-stimulus onset ($p<.05$) and involving more negative potentials for task-relevant vs. task-irrelevant faces (Fig. 2a). Computing difference waveforms between conditions clearly demonstrated a differential emotional response that preceded the modulation by task-relevance (Fig. 2b).

In addition, consistent with an attentional gating of emotional processing in the amygdala (see Pessoa, McKenna et al., 2002), neural responses during this later time interval (750-950 ms) also interacted with emotional condition: there was a reliable difference in this time-window between fearful and neutral faces when task-relevant ($p<.05$), but not when task-irrelevant (Fig. 2a, lower inset).

Because these later modulations by attention overlapped with the patient's responses (mean RT= 765 ms; see behavioral results), we also computed intracranial evoked potentials time-locked to response onset (RT). However, this analysis did not reveal any difference between experimental conditions around motor execution (or during the 200 ms pre-response time interval; see Fig. 3d). These data thus confirmed that the late LFPs modulations were driven by attention or task-related differences in stimulus processing, rather than by motor and decision-related factors, or any systematic difference in RTs for face vs. house pairs.

Discussion

By directly recording iLFPs from the left lateral amygdala of a human epileptic patient during a task where emotion and attention factors were separately manipulated (see Vuilleumier et al., 2001), we could not only test whether attended vs. unattended fearful

faces elicited a similar differential neurophysiological response compared to neutral faces in the amygdala or not, but also determine the exact latency and duration of this response. Based on previous fMRI results (Vuilleumier et al., 2001; Vuilleumier et al., 2004) as well as findings from scalp EEG/MEG recordings during emotion face processing (see Halgren, Raij, Marinkovic, Jousmaki, & Hari, 2000; Pourtois, Dan, Grandjean, Sander, & Vuilleumier, 2005; Vuilleumier & Pourtois, 2007; Eimer & Holmes, 2007), we hypothesized that an early effect of fearful faces might arise in the amygdala, regardless of whether these were task-relevant or irrelevant, and that this may occur with a distinct but later effect of selective attention.

Our new iLFPs findings confirmed this assumption and revealed that both task-relevant and task-irrelevant fearful faces elicited an early differential response compared to neutral faces in the lateral amygdala. In the main attention experiment, we found that the amplitude of iLFPs was more positive from 140 until 290 ms post-stimulus onset for fearful relative to neutral faces ($p<.01$), irrespective of attention condition, and this emotion effect was equally present for three adjacent electrodes in the amygdala (Fig. 3abc). The electrophysiological properties and time-course of this activation to fearful faces in our patient were very similar to previous intracranial ERP results obtained in the amygdala of four epileptic patients who were also studied during a face perception task after implantation of depth electrodes (see Krolak-Salmon et al., 2004 and Fig. 1c and Fig. 2a). Our single-trial decompositions (Fig. 1d and Fig. 2c) verified that this early emotion effect was stable and robust, and could be replicated at the single-trial level without any significant habituation of the neural response as a function of time (see Phillips et al., 2001). An additional ROC analysis could further establish that the

amplitude of neural responses for single trial data during this time-interval was reliably different between fearful vs. neutral faces (see Fig. 3e). In addition, our recording sites in the lateral amygdala could be characterized as being truly face-selective (see also Leonard et al., 1985; Hoffman et al., 2007), based on the results of an independent localizer experiment contrasting neutral faces to houses, which unambiguously revealed an early differential responses between these two visual categories with a similar time-course as the early emotion effects (Fig. 1d). Taken together, these results are in line with previous imaging results suggesting a rapid and relatively "automatic" response to fearful faces in the amygdala, in the sense that it may still arise in conditions where attention is diverted away from the emotionally significant faces (see Morris et al., 1999; Dolan & Vuilleumier, 2003; Vuilleumier, 2005).

The direction of amplitude changes for this early emotion effect in the amygdala may appear surprising at first sight, given that neutral faces elicited larger (or more negative) LFPs than fearful faces. We surmise that this amplitude decrease (or relative shift in polarity) for fearful faces might reflect the activation of selective inhibitory mechanisms that exist between the lateral and the basolateral nucleus of the amygdala and could be recruited early on following stimulus onset, as previously shown in animal studies during fear conditioning (Samson & Pare, 2006). However, it remains difficult to draw definite conclusions from changes in the absolute amplitude (or shifts in the polarity) of intracranial LFPs (as recorded in this study), given that they capture global neurophysiological changes at a macroscopic level (i.e. neuronal ensemble probably spanning several millimeters). This is unlike animal studies that focus on a much lower level of synaptic changes (measured from single cells) in anatomically distinct nuclei of

the amygdala (such as the basolateral and central nucleus; see Samson & Pare, 2006). Because we could not record neural activity separately from different nuclei of the left amygdala in this study, some caution is therefore needed in the interpretation of this amplitude difference reflected by these iLFPs, and no firm conclusion can be drawn from the specific direction of voltage changes between conditions. Thus, the most important and new result of our study is to reveal for the first time a distinct time-course in the differential neural activity evoked by emotion and attention within the amygdala nuclei, suggesting separate mechanisms for emotional vs. attentional effects on face processing in this region. The early emotional effect in the amygdala arose prior to, and independent of, attentional modulation based on current spatial focus. Unlike the early modulation by emotion starting at 140 ms post-stimulus onset, the modulation by attention was observed much later, becoming significant only after 700 ms and persisting for more than 300 ms afterwards (Fig. 2a). Interestingly, our data reveal that this late modulation did not only involve a main effect of spatial attention enhancing the neural response to relevant faces relative irrelevant faces, but also entailed a selective gating of the processing of fearful expression. Thus, consistent with previous fMRI results (Pessoa, McKenna et al., 2002), the difference between fearful and neutral faces was only detected when these faces were task-relevant but abolished when these faces were task-irrelevant, consistent with a gating of the emotional response in amygdala. Note that this modulation is much later than the effects of attentional selection on sensory responses in extrastriate visual cortex (typically starting around ~150-200 ms, see Desimone & Duncan, 1995; Luck, Woodman, & Vogel, 2000) and might therefore correspond to other task-related differences in processing the emotional significance of faces, which would be consistent with a similar

late latency (600-800 ms) for intracranial electrical responses of the amygdala to emotional word meaning (see Naccache et al., 2005). Hence, a late attentional gating in the amygdala might potentially be secondary to attention selection taking place in the cortical visual pathways, rather than corresponding to a direct site of attentional selection.

Noteworthy, we could rule out the alternative account that the late attentional effect in the amygdala was related to overt motor preparation or decision. When we computed intracranial evoked potentials time-locked to response onset (RT, see Fig. 3d), we failed to find any difference between experimental conditions around motor execution (or during the 200 ms pre-response time interval; see Fig. 3d), despite the substantial overlap between RTs and this late attentional effect (see Fig. 1b and behavioral results). These control analyses therefore corroborated the assumption that the late LFPs modulations were driven by attention or task-related differences in stimulus processing, rather than by motor and decision-related factors, or any systematic difference in RTs for face vs. house pairs.

There is a wealth of human brain-imaging research showing that amygdala activity may be augmented in some psychiatric disorders, particularly anxiety and depression, and this increase has usually been linked to impaired control exerted by specific regions of the prefrontal cortex, including both ventromedial and dorsolateral prefrontal areas (see Drevets, 2000, 2003). In line with this view, our new results, showing a differential time-course of emotional vs. attentional effects in amygdala, may suggest that depression (and more generally, mood disorders) could potentially affect emotion processing in at least two different ways, implicating either the early automatic responses (due to instrinsic changes in amygdala responsivity), or the subsequent gating

exerted by attention during a later time period (presumably reflecting feedback control from prefrontal regions), or both. It is possible that a reduced gating of emotion by selective attention due to impaired prefrontal activity might contribute to exacerbate emotion responses in the amygdala during pathological mood conditions, including (major) depression. Such mechanisms could thus potentially account for the dysregulation of negative affect typically associated with depression, including the inability to disengage attention from negative emotional stimuli (see Koster et al., 2005). Future studies should address this question, and test more precisely how depression may affect both the early (emotional) and later (attentional) stage of information processing within the amygdala.

There are a several caveats related the present methodology (single-case study of an epileptic patient), which have to be evoked. First, because we recorded iLFPs from the left amygdala of a single epileptic patient, a straightforward generalization of these statistical results to the (healthy) population was not feasible. Moreover, this patient had a clear epileptic history and accordingly, was treated with anti-epileptic drugs prior to our intracranial testing, which may have also affected normal brain functions. Moreover, because we did not record single-neuron firing rates (see Fried et al., 1997) but iLFPs that primarily reflect dendritic inputs rather than spiking output (Logothetis et al., 2001), it is possible that some aspects of amygdala processing (e.g., attentional gating) might not be fully captured by the present results. However, LFPs are known to correlate with fMRI BOLD signal (Logothetis et al., 2001), and thus our results clearly demonstrate a temporal dissociation between emotion and attention effects on amygdala inputs that could not be resolved by previous fMRI studies. Moreover, these effects were recorded

from lateral electrodes (Fig. 1a), consistent with anatomical data indicating that the lateral nucleus is the main entry of most sensory inputs into the amygdala (Samson & Pare, 2006).

More generally, our findings show that visual information about facial expression may reach the amygdala rapidly after stimulus onset (~140 ms, see also Halgren et al., 1994; Krolak-Salmon et al., 2004), a latency similar to early emotional responses recorded over anterior scalp regions by surface EEG (Pourtois & Vuilleumier, 2006; Eimer & Holmes, 2007), and suggest that some emotional appraisal may take place in the amygdala irrespective of whether stimuli are task-relevant or not (see also Vuilleumier et al., 2003), prior to or in parallel with face-specific responses in visual cortex that arise typically around 150-300 ms (Allison et al., 1994; Bentin, Allison, Puce, Perez, & McCarthy, 1996; Allison, Puce, Spencer, & McCarthy, 1999). When comparing these results with our "localizer" experiment, it is interesting to note that the onset of this early emotional effect (fearful vs. neutral faces) occurred during the same temporal window as the onset of category-specific effects (faces vs. houses, 136 ms, see Fig. 1c).

Taken together, the present findings are consistent with separate influences of attention and emotion on stimulus processing (Vuilleumier et al., 2001; Keil, Moratti, Sabatinelli, Bradley, & Lang, 2005; Vuilleumier, 2005), but also help reconcile discrepant findings of previous fMRI studies. Some have reported emotional responses without attentional modulation in amygdala (e.g. Vuilleumier et al., 2001; Vuilleumier et al., 2004), while others found significant modulations by attention (e.g. Pessoa, McKenna et al., 2002). Our new data indicate that both emotion and attention effects take place in the lateral amygdala but at different latencies. It is possible that different experimental

designs (e.g. blocked, see Pessoa, McKenna et al., 2002 vs. event-related, see Vuilleumier et al., 2001) might lead to a different sensitivity of fMRI BOLD measures to the early and late phases of amygdala activation. More generally, our findings highlight the importance of tracking the precise time-course of neural activity (beyond current fMRI techniques) to better understand brain function.

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Figures legend

Figure1. (a) Left back and top-view of the patient's brain (T1 MRI reconstructed volume), showing the exact location of the 3 recorded sites from an intracranial electrode implanted in the left medial temporal lobe and reaching the amygdala, as confirmed by coregistration of MRI and CT scans post-implantation. These three electrodes showed distinctive responses to faces as compared to houses. Their Talairach coordinates estimated after normalization of brain scans overlapped with the lateral and/or basolateral nucleus of the amygdala (from medial to lateral electrodes: -22x, -7y, -18z; -26x, -6y, -18z; and -31x, -6y, -18z, respectively) in accordance with results from human imaging studies (Zald, 2003). **(b)** Mean reaction times (± 1 s.e.m) obtained in the main attention experiment. Statistical analysis of these behavioral data showed significant main effects of emotion and attention but no interaction, consistent with previous results in this task (Vuilleumier et al., 2001). **(c)** Average intracranial amygdala responses (average of all three recording sites) to faces (red trace) and houses (blue trace) as obtained in the independent "face localizer" experiment. Randomization tests confirmed that responses to faces differed from those to houses during three time-windows following stimulus onset (see results), with the earliest difference starting 136 ms post-stimulus onset. **(d)** ERP image (amplitude×time representation of all consecutive trials, see Delorme & Makeig, 2004) from the localizer experiment (lateral electrode). Differential responses to faces (n=28 trials) and houses (n=28 trials) arose during three successive time-windows (as confirmed by statistical permutation tests), spanning from 136 to 710 ms post-onset, and remained generally stable across the successive trials.

Figure2. (a) Average local field potentials (all 3 electrodes collapsed) for each condition in the main experiment, showing responses to fearful faces (red lines) and neutral faces (blue lines) when task-relevant (thick lines) or task-irrelevant (thin lines). A similar time-course was observed for fearful faces during the earliest electrical deflection (peaking around 200 ms), regardless of whether faces were task-relevant or not (see inset above). By contrast, the later negative deflection (peaking between 700-800 ms) was enhanced when faces were task-relevant (regardless of expressions), and showed a larger difference between fearful and neutral expressions for task-relevant than task-irrelevant faces (see inset below), consistent with a delayed gating of emotional responses by attention. For each inset, statistical differences ($p<.05$) were highlighted by a * symbol. **(b)** Difference waveforms computed between conditions showing the main effect of emotion (subtraction between neutral and fearful faces; orange line) and the main effect of attention (subtraction between task-relevant and task-irrelevant faces; black line). An emotional modulation was clearly seen from 140 ms onwards, while the attentional modulation became visible only later, around 710 ms post-stimulus onset. **(c)** ERP image for all trials in the main experiment (lateral electrode), sorted according to the four different conditions. A biphasic negative deflection occurred from ~120 to ~500 ms post-onset for all stimuli (n= 28 trials for fearful task-relevant, 24 neutral task-relevant, 32 fearful task-irrelevant, and 29 neutral task-irrelevant). Significant amplitude difference (confirmed by statistical permutation tests) were found between emotion conditions (fearful vs. neutral faces) during an early time-window (140-290 ms), and followed by differences between attention conditions (task-relevant vs. task-irrelevant faces) during a later and longer time-window (750-950 ms).

Figure3. (a) Average local field potentials time-locked to the stimulus onset for each condition in the main experiment shown for the more medial electrode site (Talairach coordinates: -22x, -7y, -18z), as well as for **(b)** the intermediate electrode site (Talairach coordinates: -26x, -6y, -18z) and **(c)** the more lateral electrode site (Talairach coordinates: -31x, -6y, -18z), showing consistent responses to fearful faces (red lines) and neutral faces (blue lines) when task-relevant (thick lines) or task-irrelevant (thin lines) at each recording sites in the amygdala. **(d)** Average local field potentials (all 3 electrodes collapsed) time-locked to the response onset, showing no clear or systematic response-related intracranial ERP components, and thus indicating that responses in the lateral amygdala after stimulus onset (**abc**) were not due to decision or motor factors. **(e)** Receiver operating curve (ROC). We computed the mean amplitude of neural responses for each individual trial in the 140-280 ms time-interval post-stimulus (corresponding to the emotion effect, see Fig. 2a) and submitted these values to a ROC analysis contrasting fearful to neutral faces (irrespective of whether they were task-relevant or task-irrelevant). This analysis confirmed that the amplitudes of neural responses for single trial data during this time-interval were reliably different between fearful vs. neutral faces (see results).

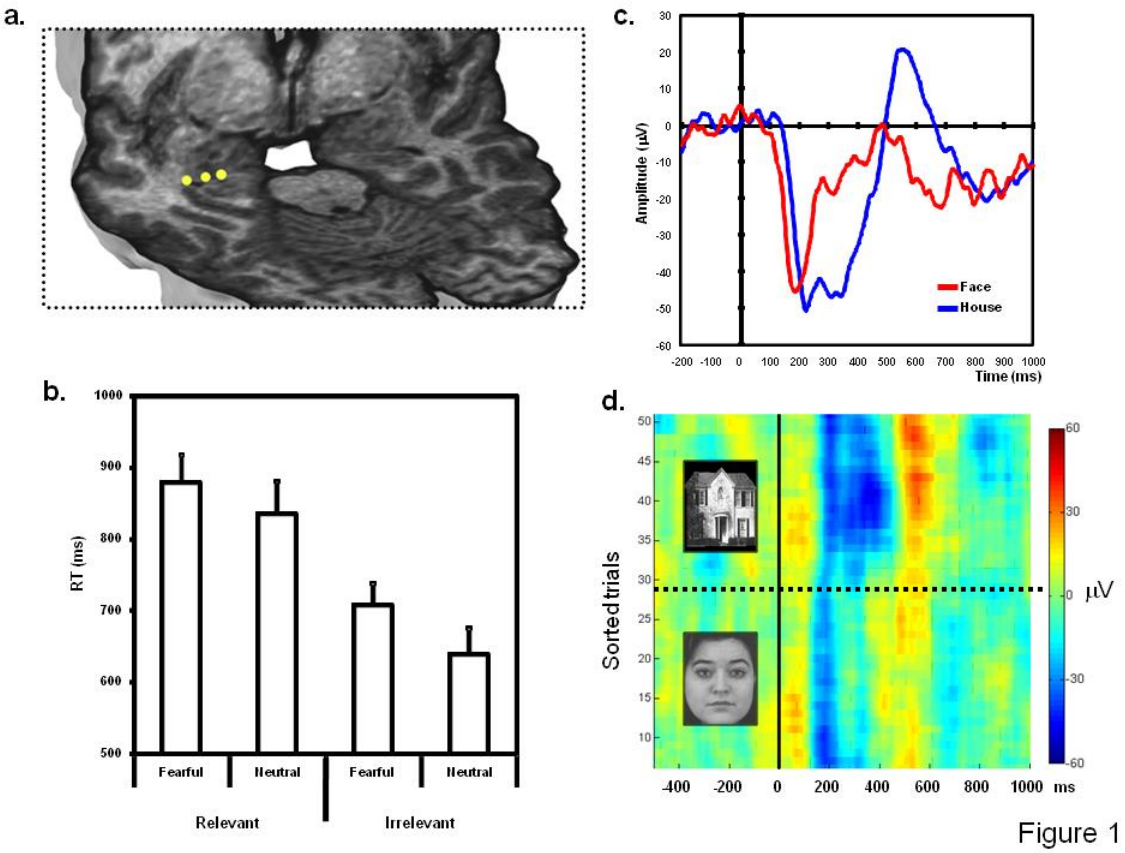
a.
c.
Amplitude (μV)
Time (ms)
Face
House
b.
RT (ms)
Fearful
Neutral
Fearful
Neutral
Relevant
Irrelevant
d.
Sorted trials
μV
ms

Figure 1

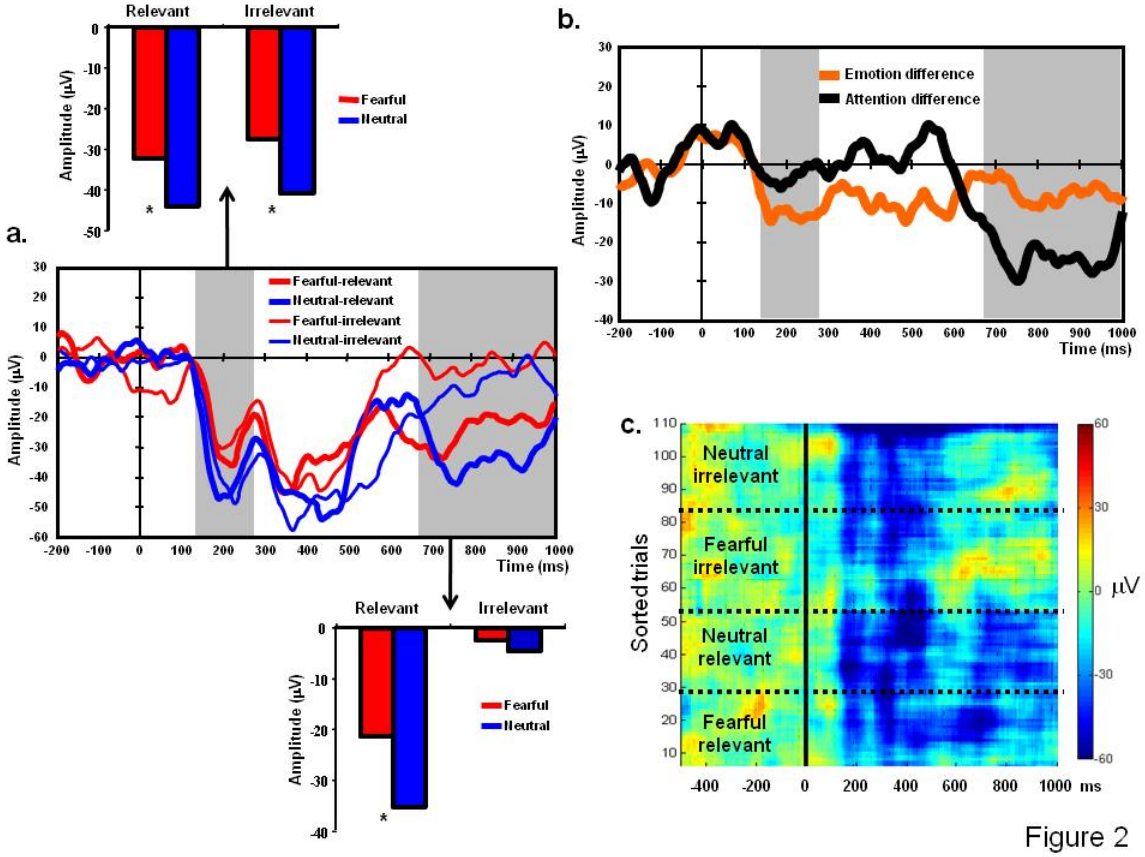
a.
Relevant
Irrelevant
Amplitude (μV)
Fearful
Neutral
Fearful-relevant
Neutral-relevant
Fearful-irrelevant
Neutral-irrelevant
Time (ms)
b.
Emotion difference
Attention difference
c.
Neutral irrelevant
Fearful irrelevant
Neutral relevant
Fearful relevant
Sorted trials
μV
ms

Figure 2

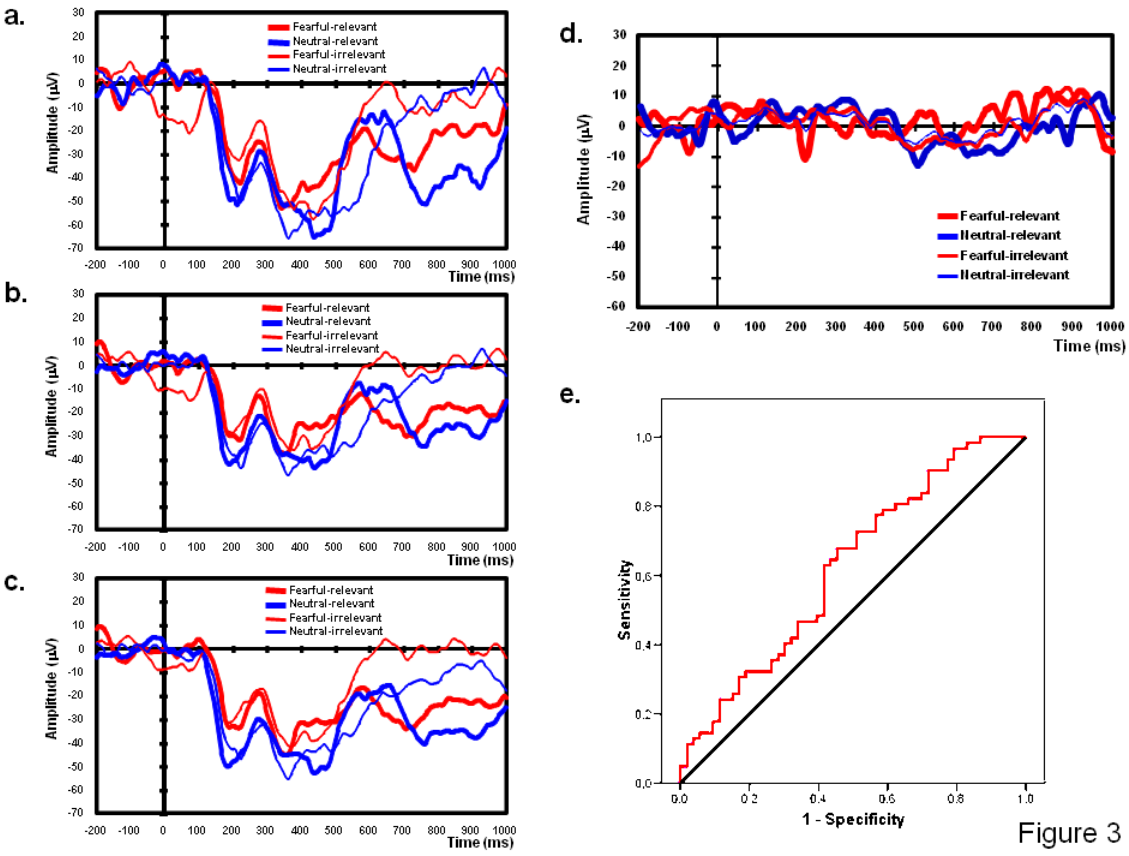
a.
b.
c.
d.
e.
Fearful-relevant
Neutral-relevant
Fearful-irrelevant
Neutral-irrelevant
Amplitude (μV)
Time (ms)
Sensitivity
1 - Specificity

Figure 3